REMARKS

The present paper is submitted in response to a notice of non-compliant amendment dated July 1, 2010 which related to an improper identifier being used in the claims. This response is timely filed. The below remarks are made in response to the office action dated December 17, 2009, and are identical to the remarks previously transmitted.

A. Status of claims and Response to Claim Objections

Claims 23, 25, 26, 28, 32 and 127 are pending in the application and stand rejected under 35 U.S.C. 103(a) and 35 U.S.C. 112, second paragraph. The Office action further denied the benefit of priority to Provisional application 60/435,827.

Claim 32 has been cancelled herein above. This renders moot the rejection under 35 U.S.C. 112, second paragraph

B. Priority

The Examiner rejected the Applicants claims to benefit of priority of U.S. Provisional application 60/435,827 stating that the prior filed application "fails to provide adequate support or enablement for one or more of the claims." The Examiner contends that the description of use of small interfering RNAs at page 8 is not sufficient and that "there is nothing whatsoever that provides "adequate" support/enablement for the claimed chronic inflammation treatment methods". The Examiner then goes on to take particular issue with the claims because in the specification of the priority

document "there is nothing whatsoever that indicates that the inventors were in possession of … siRNA targeted against the nucleotide sequence encoding amino acids 1-65 of SEQ ID NO:4."

Typically, an earlier filed domestic application is not examined to determine whether a party is entitled to the benefit of an earlier filing date except when the earlier filing date is actually needed. *In re Shaw* 202 USPQ 285, 292 (Comm'r Pat 1978). Moreover, it is well-established that an Applicant may be entitled to the benefit under §119 or §119 as to one claim and not for another claim. Here the Examiner appears to have rejected the priority benefit for all of the claims forcing applicants to fight a written description and enablement battle based on the priority application. However, the Examiner's reasoning seems to focus on the subject matter of 127. In the following discussion, Applicants show that the claims are entitled to the benefit of priority of U.S. Provisional Application 60/435,827. Given this discussion, Applicants believe that because at least one claim is entitled to claim the benefit of priority of U.S. Provisional Application 60/435,827, the Examiner should withdraw the objection to the priority claim.

i. The claims have written description support in the specification

Claim 23 recites:

> A method of inhibiting inflammation, said method comprising:
>
> identifying a subject having symptoms of a condition associated with chronic inflammation; and

> reducing in said subject the level or activity of the nuclear factor high endothelial venule (NF-HEV) polypeptide or a biologically active fragment thereof, thereby inhibiting the inflammatory response in endothelial cells of said subject
>
> wherein said reducing comprises reducing the expression of a nucleic acid of SEQ ID NO:1 by administering to said subject an siRNA complementary to at least a portion of SEQ ID NO:1 in an amount effective to reduce the expression of NF-HEV polypeptide encoded by said nucleic acid of SEQ ID NO: 1.

The issue of whether a patent specification adequately describes the subject matter claimed is a question of fact. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The written description requirement is intended "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In order to meet the written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Alternatively stated, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas- Cath*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Moreover, "[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by- case basis." *Eiselstein v. Frank*, 52 F.3d 1035, 1039, 34

USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas- Cath, 935 F.2d at 1561, 19 USPQ2d at 1116).

Thus, the law establishes that written description for a claim is separate and distinct from any other requirement under 112 (i.e., separate from enablement and separate from the best mode). Put in layman's terms, the written description requirement asks that question "Did the Applicants write down their invention" or "Did they articulate it in the specification" in such a way that the skilled person could review the specification and understand that the inventor had the invention in mind. This first step is a subjective requirement looking at whether the Applicant provided the text for the claimed invention. The next step, objective step i.e., the step "in such a manner as to enable the skilled person to make and use the invention" is the step of enablement and is addressed below. Dealing first with the issue of description, the Applicants have clearly articulated each element of the invention in the Provisional application.

Referring to page 8 of the specification which the Examiner also has pointed out, the specification states that the invention provides: "a method of modulating the expression of a gene in an endothelial cell comprising inhibiting … **the expression of NF-HEV**" and that the inhibiting "**may comprise providing … small interfering RNAs that induce degradation of a NF-HEV mRNA**." The specification at the same page shows that chronic inflammatory disorders involve development of HEV-like vessels. The specification goes on to specifically provide the sequence of SEQ ID NO:1 as the polypeptide sequence of NF-HEV and that inhibition of expression of this protein is desired because such inhibition will inhibit development of HEV-like vessels and

therefore be useful for treating development of HEV-like vessels in for example chronic inflammatory disorders. In addition, page 12 of the specification shows written description specifically of "amino acids 1-65 of SEQ ID NOs 4-6." These descriptions in the specification certainly articulate that inhibition of expression of SEQ ID NO:1 including that portion that encodes amino acids 1-65 of SEQ ID NO:4 is desired and can be done with siRNA. This simple articulation should meet the written description aspect of 35 U.S.C. 112 leading to the next question of enablement.

ii. the claims are enabled in the priority document

The enablement requirement relies on not just the specification of the application but also on the level of ordinary skill in the art. In determining enablement, it is well understood that the specification need not teach and preferably should omit that which is known in the art and the Examiner should consider not just the original disclosure but all evidence of record weighing evidence that supports enablement against that which does not. Whether experimentation is undue is not a simple single factual determination but instead looks to nature of the invention; state of the prior art; predictability of the art; amount of guidance available, presence or absence of working examples, breadth of the claims, relative skill of those in the art and quantity of experimentation needed. It is improper to conclude that the specification is not enabled based on just one of the above features, but instead the enablement analysis should be made viewing the invention as a whole.

In the present instance, the Examiner herself has cited compelling evidence that the state of the art and the level of skill of those in the art is such that taking the written written description in the specification that an siRNA complementary to at least a portion of SEQ ID NO:1 should be used to reducing the expression of a nucleic acid of SEQ ID NO:1 and thereby treat inflammation, the skilled person would have been able to make and use the invention. Referring to the Examiner's arguments cited in the obviousness rejection, the Examiner stated that "Lewis et al teach that one can make a target-specific siRNA compound and use it to inhibit/target expression in a mammal for therapeutic applications" [the Examiner points to paragraphs 0008-0009; 0018-0019; 0033-0037, 0042-0045 and 00197 of U.S. 2003/0143204). Likewise, Elbashir et al. also cited by the Examiner provides "guidelines one can follow to design effective siRNA molecules such that one selects an "5'-AA(N19)UU" or "5'-AA(N21)" sequence motif having about 32-79% GC content with the coding region of a target mRNA beginning from about 50-100 nucleotides downstream of the start codon." The Examiner states that Elbashir demonstrate the efficacy of siRNA techniques. Clearly, if these teachings cited by the Examiner are sufficient to support an obviousness argument, it stands to reason that the level of skill in the art, the state of the prior art, and the quantity of experimentation and the nature of the invention is such that that the skilled person at or around the time of filing of the present application was sufficiently skilled to be able to make a target-specific siRNA compound if that individual is given the target at which to direct the siRNA compound.

In the present case, the nature of the invention is simply to treat a inflammation by providing siRNA compounds directed against a sequence of SEQ ID NO:1. the specification of the priority document provides a detailed description of SEQ ID NO:1 and also directs the skilled person to prepare siRNA compounds against this target. As articulated by the Examiner, references such as Lewis et al. and Elbashir et al provide ample evidence that once that direction is given the skilled person would be able to prepare the siRNAs. The fact that some experimentation will be used is not fatal to enablement. Indeed, extensive quantity of experimentation can be carried out as long as it is not undue. Here it would not be undue because the art shows how to make siRNA molecules and indeed how to test them. Nothing more is needed. The mere fact that a specific working example is not presented in the priority document does not detract from the fact that the claims as a whole were enabled because the presence of working examples, while useful in the enquiry is not an absolute requirement and indeed examples can be prophetic or not present at all.

iii. invention as a whole is supported by the priority document

In view of the above discussion, the invention as a whole is sufficiently supported by the disclosure of U.S. Provisional Application 60/435,827 and as such, the present invention should be accorded an effective filing date of **December 19, 2002** which is the filing date of the aforementioned provisional application.

C. Objection to claims

The Examiner objected to claims 23, 25, 26, 28, 32 and 127 for reciting the abbreviation NF-HEV. The amendment to claim 23 spelling out the full term obviates the grounds for objection.

D. Rejection of Claim 32 under 35 U.S.C. 112, second paragraph

Claim 32 was rejected under 35 U.S.C. 112, second paragraph. The claim has been cancelled rendering further comment on the rejection moot.

E. Rejection of Claims under 35 U.S.C. 103

Claims 23 and 25 were rejected under 35 U.S.C. 103 over a combination of King et al. U.S. 2002/0131971 (published September 19, 2002) in view of Lewis et al. US 2003/0143204 (published July 31, 2003).

Claims 23, 25 and 127 were rejected under 35 U.S.C. 103 over Lipman (Current Rheumatology Reports, 2001 3:513-519) in view of Woolf et al. (US 2007/00151445) and Elbashir et al. (Methods 2002, 26:199-213).

Claims 23, 25-26, 28, 32 and 127 were rejected under 35 U.S.C. 103(a) over Onda et al. (*J. Cerebral Blood Flow & Metabolism*, 1999, 19:1279-1288) in view of GenBank accession Nos AB024518 and BAA75892), Lewis et al. (US 2003/0143204) and Elbashir et al (Methods 2002, 26:199-213).

Applicants respectfully traverse each of the rejections and request reconsideration thereof in view of the following remarks.

i. Rejection based on a combination of King et al. U.S. 2002/0131971 (published September 19, 2002) in view of Lewis et al. US 2003/0143204 (published July 31, 2003).

The Examiner rejected claims 23 and 25 over a combination of King et al (US 2002/0131971) and Lewis et al (2003/0143204). According to the Examiner King et al has teaching that one of numerous references encodes a DSV27-related protein. However , the Examiner readily admits that King provides no description of treatment of inflammation. The entire disclosure of King relates to 1896 sequences that are used by King for the therapy and diagnosis of cancer, particularly colon cancer. Adding to this deficient disclosure the teachings of Lewis does little to render obvious the claims of the present invention. Lewis is simply a generalized discussion of inhibiting gene expression using double-stranded nucleic acids. When the Lewis disclosure becomes more specific it states that "Specifically, gene expression is inhibited relating to bacterial infection such as anthrax or related to a viral infection such as small pox". In the 198 paragraphs of discussion in Lewis, there is only one mention of inflammatory diseases and that is found at paragraph 009 in the background discussion simply stating that "Inhibiting such genes as cyclooxygenase or cytokines could also treat inflammatory diseases such as arthritis". Nothing anywhere in the combined disclosure of King and Lewis would have motivated the skilled person to consider using siRNA against NF-HEV to reduce in said subject the level or activity of the NF-HEV polypeptide and thus

ameliorate the symptoms of a condition associated with chronic inflammation. Moreover, reviewing other teachings cited by the Examiner, e.g., Kasuya that the Examiner previously cited, it is apparent that those of skill in the art merely understood that expression of DVS 27, changes in response to unidentified "inflammatory stimuli," without any indication of the function of that compound.

In contrast to the teachings of King and Lewis, and the general teachings in the art of lack of known function of DVS 27, the present specification for the first time demonstrates specifically that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV ameliorates symptoms of a condition associated with chronic inflammation. For example, the specification demonstrates that NF-HEV induces the expression of several pro-inflammatory chemokines, including CCL2/MCP1, and, conversely, that reducing the level or activity of NF-HEV reduces the level or activity of these pro-inflammatory chemokines. *See*, *e.g.*, paragraphs [0038], [0055], [0382], [0449], and [0452].

Because the combination of King and Lewis does not establish the nexus between decreasing expression levels of HF-NEV and chronic inflammation, that combination does not render obvious claims 23 and 25. The applicants request that the rejection based on King and Lewis be withdrawn.

ii. Rejection based on a combination of Lipman in view of Woolf et al. (US 2007/00151445) and Elbashir et al.

The combination of Lipman, Woolf and Elbashir was cited to supposedly render obvious claims 23, 25 and 127. Applicants respectfully traverse this rejection.

In this section, the Examiner bases the obviousness argument on the assertion that while Lipman does not teach ameliorating pain with an siRNA targeted to a gene encoding SEQ ID NO:4 and Elbashir simply is a teaching of how one would make siRNA molecules, the skilled person would be driven to sift through 14715 sequences in Woolf to find a sequence that matches SEQ ID NO:4 of the present invention. Why? As an initial matter, the claims of the present invention relate to the treatment of **inflammation** whereas the Examiner's arguments are based on a combination of references that discuss amelioration of pain. Pain and inflammation, while they may occur together in many clinical situations are not necessarily one and the same symptom. There is no evidence that a reduction in pain will produce a reduction in inflammation or vice versa in all circumstances and this nexus certainly does not appear in the references combined in the instant rejection. In order to clarify that the claims of the present invention are related to inhibition of an inflammation, the term "symptoms of a condition associated with inflammation" have been removed and clarified as "inhibiting the inflammatory response in endothelial cells" of said subject.

Woolf was published on January 18, 2007 more than 5 years after the priority date of the instant application. Even assuming that the disclosure of Woolf was publicly

available as of the August 14, 2002 filing date of Woolf, and even assuming that chronic pain and inflammation are one and the same disorder, which they are not, *KSR v.Teleflex* clearly states that obviousness only attaches when "there is a design need or market pressure to solve a problem and there are a **finite** number of **identified**, **predictable** solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp." Nothing in Woolf or Lipman or Elbashir shows that each of the subset of the 14715 sequences that are over-expressed in pain would in fact predictably result in a reduction in pain if targeted with an siRNA. As noted by the Federal Circuit in Eisai v. Dr. Reddy, when applying KSR v. Teleflex in a chemical case:

> The Supreme Court's analysis in KSR thus relies on several assumptions about the prior art landscape. First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that

> the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." ***To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable***

The present case is indeed one such case where the potential solutions form a combination of the **entire** teachings of the art would lead to a genuine predictability. There is no reason that the skilled person reviewing the whole of the disclosure of Woolf would specifically pick out SEQ ID NO:11450 out of the 14715 sequences therein to focus on for the treatment of pain and there is certainly nothing in that combination that specifically points to the treatment of ***inflammation*** to which the present claims are directed. There is nothing in Woolf that shows that SEQ ID NO:11450 in particular has some particular features or properties that would set it apart from the numerous other alternatives in that document to render it the chemical entity of choice when choosing to design a chronic pain therapy.

Moreover, other references that the Examiner has previously cited show that at the time the present application was filed there remained some vacillation as to the role

of DVS 27 even in pain. For example, while Kasuya et al and Onda et al each cited by the Examiner, both make some generalized speculation that DVS 27 could be involved in inflammation they each specifically concede that the functional role of DVS 27 was not then known. *See* Kasuya, page 16, col. 2; see also Onda et al. which states "Although its functional role still is unknown, the DVS 27 gene was found to encode a nuclear protein that could be involved in inflammatory events". Indeed, reviewing Kasuya that the Examiner previously cited, it is apparent that those of skill in the art merely understood that expression of DVS 27, changes in response to unidentified "inflammatory stimuli," without any indication of the function of that compound. In contrast, the present specification for the fist time demonstrates that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV ameliorates symptoms of a condition associated with chronic inflammation. For example, the specification demonstrates that NF-HEV induces the expression of several pro-inflammatory chemokines, including CCL2/MCP1, and, conversely, that reducing the level or activity of NF-HEV reduces the level or activity of these pro-inflammatory chemokines. *See*, *e.g.*, paragraphs [0038], [0055], [0382], [0449], and [0452].

Reviewing the entire teachings of art cited by the Examiner, it remains unpredictable that the person skilled in the art would specifically select DVS 27 to target with siRNA for the treatment of chronic pain. Hence the combination of Lipman, Woolf and Elbashir does not render obvious the claims of the present application.

iii. Rejection based on a combination of Onda et al. in view of Genbank Numbers AB024518 and BAA75892 in view of Lewis et al (US 2003/00143204) and Elbashir et al.

The Examiner relies on Onda as the primary reference in this rejection. The reach of this reference does not stretch to supporting obviousness of the present claims which relate to methods for the treatment of chronic inflammation. Again, Applicants believe that amendment of the claim to clarify that the method claimed is for the reduction/inhibition of inflammation removes the ground for rejection based on Onda. The discussion in Onda regarding DVS27 is as follows:

> "One of the unknown genes, DVS 27, whose expression was most highly upregulated in vasospastic arteries, has been cloned and partially characterized by analyses of intracellular localization of the protein and changes of the expression levels in response to inflammatory stimuli. Although ***its functional role still is unknown***, the DVS 27 gene was found to encode a nuclear protein that could be involved in inflammatory events. Thus, such an approach will be useful, at least in part, to predict the role of proteins encoded by the unknown genes"

This sole paragraph of Onda relating to DVS 27 provides no indication of whether DVS27 has pro-inflammatory or anti-inflammatory activity. Onda et al. reported that DVS27 mRNA is induced in hemorrhagic cerebral vasospastic arteries. However, these vessels are clearly distinct from the High Endothelial Venule (HEV)-like vessels that are

typically associated with chronic inflammation in various tissues (Hemorrhagic cerebral vasospastic arteries are not HEV-like vessels because HEV-like vessels are post-capillary venules whereas the vessels described by Onda are arteries and not venules). Onda et al. also provides no indication at all that in order to modulate **chronic inflammation** such as that seen in rheumatoid arthritis, Crohn's disease or inflammatory bowel disorder, DVS27 should be inhibited or otherwise downregulated. In the absence of such a suggestion in Onda, we must look to the other references cited by the Examiner in the combination to see if they overcome this flaw. They do not. Lewis simply is a generalized discussion of inhibiting gene expression using double-stranded nucleic acids. It focuses on inhibition of gene expression in anthraz or viral pox infection. There is nothing in Lewis that would motivate the skilled person to look to inhibiting DVS 27 expression for treating chronic inflammation. Indeed the only mention in Lewis of inflammatory disease is a sentence in the background that states “Inhibiting such genes as cyclooxygenase or cytokines could also treat inflammatory diseases such as arthritis”. Nothing in the combination of Onda and Lewis, or Onda, Lewis and Elbashir shows that the DVS 27 is a cyclooxygenase or a cytokine. Therefore, the claims of the present invention which are specifically directed to siRNA based inhibition of SEQ ID NO:4 cannot be rendered obvious by the combination cited by the Examiner.

As recognized by the examiner, “Onda et al do not teach inhibiting the inflammatory activity of DVS27 with a DVS27 specific siRNA in a subject having chronic inflammation to ameliorate the symptoms of the inflammation in the subject”. Indeed, there is no teaching in Onda or anything else cited in the Office action that DVS 27 has pro-inflammatory activity. Thus, the sole paragraph in Onda that simply states that

DVS27 has been "cloned and partially characterized by analyses of intracellular localization of the protein and changes of the expression levels in response to inflammatory stimuli" is a statement made in a vacuum. There is no indication whether DVS 27 induces a pro-inflammatory or anti-inflammatory response. In contrast, the present specification demonstrates that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV will be useful in the inhibition of inflammation. For example, the specification demonstrates that NF-HEV induces the expression of several pro-inflammatory chemokines, including CCL2/MCP1, and, conversely, that reducing the level or activity of NF-HEV reduces the level or activity of these pro-inflammatory chemokines. *See*, *e.g.*, paragraphs [0038], [0055], [0382], [0449], and [0452].

It was the teachings of the present invention that first demonstrated that NF-HEV has pro-inflammatory properties and that reducing the level or activity of NF-HEV ameliorates symptoms of a condition associated with inflammation. Only with this teaching would a person of ordinary skill in the art be motivated to inhibit inflammation by identifying a subject having symptoms of a condition associated with chronic inflammation and reducing in the subject the level or activity of the NF-HEV polypeptide.

Therefore, for at least the reasons discussed above, Applicants respectfully submit that claims presented herein above are not obvious over Onda in view of Lewis and Elbashir. Applicants respectfully request that the rejection of claims 23-25, 28-31, and 127 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

F. Concluding remarks

Applicants believe that the above response shows the non-obviousness of the claims of the present invention and provides a clear showing of the support for the present claims in the priority document. Applicants have also addressed the rejection under 35 U.S.C. 112 second paragraph and hence believe the claims of the present invention are in condition for allowance. Applicants respectfully request that the Examiner considers such favorable action.

The Commissioner is authorized to charge any additional fees or credit any overpayment to the Deposit Account of McAndrews, Held & Malloy, Account No. 13-0017.

Dated: July 27, 2010

Respectfully submitted,

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